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An ASIC Channel for Acid Chemotransduction

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Spontaneous breathing requires feedback controls in which detection of blood gas and pH are critical. While O₂ detection is performed by peripheral chemoreceptors, CO₂/pH-sensitive chemoreceptors are in the carotid bodies (CBs), but major sites are also within the brain (the central chemoreceptors [CCR]). CO₂/pH signals are related to the acid-base status of the blood and reflect the adequacy of breathing to metabolism. Small changes in CO₂/pH can affect breathing, so that a rise in PCO₂ as small as 1 mm Hg produces an evident change in ventilation.¹ Such a high CO₂ sensitivity relies in the inherent properties of CO₂/pH-sensing molecules present both in CB and CCR cells, as shown in several recent studies on CO₂/pH sensing ion channels and receptors.^{2,3} Functional properties of most proteins can be regulated by changes in pH, as this would only require 1 or a few titratable residues of the molecule, whose protonation can lead to conformation changes that translate into changes in activity. However, to define whether those molecules have a relevant role in CO₂/pH chemoreception, some more criteria should be met, including their range of pH sensitivity, their location in chemoreceptor cells, and their functional contribution to the integrated chemoreceptor response. In this regard, the molecular characterization of pH-sensitive channels and transporters has progressed considerably within the last years, but conclusive evidences of their contribution to acid chemotransduction are not so well established for many of them. The main reason for this delay is the fact that the identity of the primary sensory cells constituting CCRs and of their neuronal networks remains elusive. In vitro, neurons from many brain locations are excited or inhibited by CO₂/pH changes, but it has been difficult to link this neuronal chemosensitivity to chemoreception in vivo. Moreover, in addition to chemosensitive neurons, CCRs sites may also contain neurons with other integrative functions that are not clearly distinct from chemosensitive ones in their morphological or functional properties, making their experimental study difficult.

Several members of the inward rectifier K⁺ (Kir) channels are among these pH-sensing molecules, as they have been reported to be highly sensitive to intra or extracellular pH (pH_i and pH_o) in the physiological range and also regulated by

moderate changes in CO₂ levels (see^{2,3} for review). Another group of channels involved in pH signaling are the members of the 2-pore domain K⁺ channels, that are also modulated by changes in pH_i or pH_o.⁴ Among them, TASK-1 channels have been shown to contribute to chemosensitivity of both brain stem neurons⁵ and rat CB chemoreceptor cells.⁶ Other ion channels modulated by CO₂/pH changes include voltage-activated K⁺ channels, L-type Ca²⁺ channels, pacemaker HCN channels, TRP channels, and the family of acid-sensing ion channels (ASICs).³ These amiloride-sensitive non-voltage-dependent cationic channels were originally described as transducers of pH signals in peripheral sensory neurons. They have been identified afterward in a large number of central and peripheral neurons, where they show a striking functional diversity: they modulate a wide range of sensory functions including perception of touch, taste, temperature, and pain, but they are also involved in neuronal plasticity, hence contributing to learning and memory.^{7,8}

The study performed by Tan et al⁹ in this issue of *Circulation Research* provides a new biological function to ASICs channels by demonstrating their involvement in acidic-stimuli chemotransduction in CB chemoreceptors. They report the expression of ASIC-1 and ASIC-3 in chemoreceptor cells and their contribution to cell excitability on changes in pH_o. The choice of this preparation, a chemosensitive organ with a well defined structure and function (as opposed to CCRs), allows them to gain insight into the possible physiological role of ASICs channels as chemoreceptor molecules.

The CB chemoreceptor cells are the sensory receptors for hypoxia, hypercapnia, and acidosis.^{10,11} In the case of low PO₂, the depolarizing receptor potential arises primarily from the inhibition of several classes of K⁺ conductances, which vary among different species.^{12–14} This depolarization leads to calcium entry through voltage-dependent Ca²⁺ channels and release of neurotransmitters that excite the afferent nerve terminals. The transduction mechanisms for hypercapnic and acidic stimuli in CB chemoreceptor cells have received less attention, but as these cells are easier to identify and isolate, studies on the cellular mechanisms of CO₂/pH chemoreception preceded similar studies in CCRs. There is strong evidence that these stimuli also produce inhibition of several ion channels.^{15,16} The effects of hypercapnia have long been considered to be secondary to acidification of pH_i,¹⁷ which would be the trigger of K⁺ channel inhibition, leading to membrane depolarization and voltage-gated Ca²⁺ entry.¹⁸ Several studies demonstrating that the blockade of voltage-dependent Ca²⁺ channels inhibits chemoreceptor responses to hypercapnia^{19,20} confirm their involvement in CO₂/pH chemotransduction in the CB. Although species-related differences in the molecular identity of the mechanisms involved have been reported, this general scheme holds true for several

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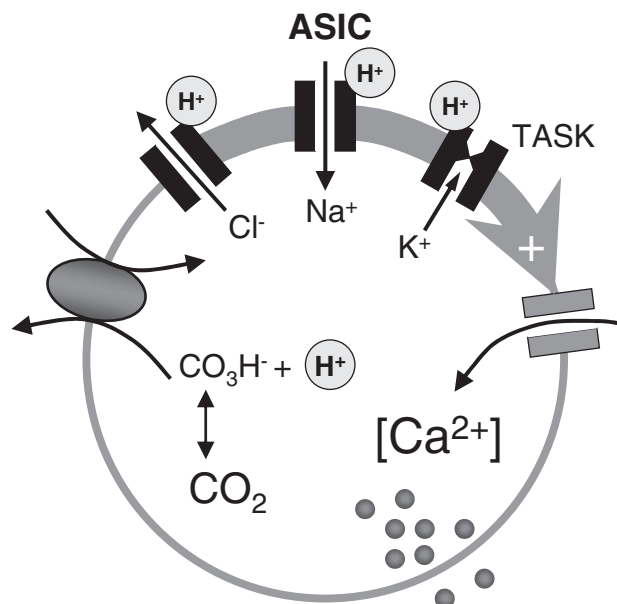


Figure. CO₂/pH sensing mechanisms identified in rat CB chemoreceptor cells (see text for details).

preparations in which CO₂/pH chemotransduction has been explored, being the rat CB the one studied in more detail.

In the rat CB, the K⁺ channel modulated by p*H*_i was initially suggested to be the maxiK (K_{Ca}) channel. However, the pH sensitivity of this channel was very limited¹⁵ and its pharmacological blockade did not depolarize chemoreceptor cells, indicating that K_{Ca} channel inhibition was not the trigger of the CO₂/pH chemotransduction cascade.¹² Ulterior studies demonstrating the presence of TASK-1 channels in rat CB and their inhibition by a fall in p*H*_o led to the proposal that both p*H*_i and p*H*_o will participate in the response to acidic stimuli.⁶ In addition to these K⁺ channels, a recent study demonstrated the presence in rat CB cells of an inwardly-rectifier Cl⁻ current activated by decreasing p*H*_o.²¹ This current was proposed to participate in intracellular acidification and membrane depolarization during acidic challenge. Extracellular acidosis, by increasing Cl⁻ conductance and decreasing TASK channel conductance, will result in plasma membrane depolarization. Moreover, the increased efflux of chloride by activation of this channel would lead to CO₃H⁻ efflux through the Cl⁻/CO₃H⁻ transporter present in chemoreceptor cells,¹⁰ resulting in a fall in p*H*_i. In this way this anion current could also contribute to the adaptation of p*H*_i to p*H*_o. However, to confirm these hypotheses, the study of the contribution of Cl⁻ channels to CB chemoreception warrants further investigation.

The present article⁹ adds a new candidate for acid chemotransduction, ASICs channels, that would be functioning best as p*H*_o sensors, as demonstrated by their lactate sensitivity. The enhancement of currents through ASICs channels in the presence of lactate has been demonstrated to be mediated by the ability of lactate to quelaate extracellular Ca²⁺. In an elegant series of experiments, Immke and McCleskey²² conclude that H⁺ open ASICs by accelerating the release of Ca²⁺ from a high affinity binding site on the external side of the pore, suggesting that this relief of Ca²⁺ blockade is in fact the

essence of ASICs gating by H⁺. This mechanism of activation may contribute to chemoreceptor selectivity, making ASICs channels more responsive to metabolic acidosis, and thus participating in the ventilatory adaptation during exercise.¹⁰

The emerging picture from these results suggests that, as in the case of other sensory modalities, there is a parallel processing for CO₂/pH detection in CB chemoreceptors, involving multiple sensors (Figure) which could be expressed in a single cell or in different cell populations. By having different preferred stimuli (respiratory versus metabolic acidosis) and different sensitivity range, they would contribute to generate adaptive respiratory responses over a broader range of CO₂/pH changes. In response to hypercapnia or acidosis, multiple signals are generated. Both p*H*_i and p*H*_o could serve as the immediate stimulus for chemoreceptors (in fact they may operate simultaneously), and even CO₂ itself could be sensed independently of p*H*_i changes.²³ In this regard, it should be noted that none of the identified sensors (Cl⁻, TASK-1, and ASICs channels) explain CB chemoreceptors response to isohydric hypercapnia, where there are not associated p*H*_o changes. Further studies along this line of research are needed to complete the identification of the molecular mechanisms involved, and to explore the possibility of additive or synergistic effects of CO₂/pH changes on CB chemoreceptors acting on different molecular targets.

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Disclosures

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